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EXAMINER	
AEDER, SEAN E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,392	YU ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-20 and 22-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *23* is/are allowed.

6)☒ Claim(s) *1,2,5-20,22 and 24-37* is/are rejected.

7)☒ Claim(s) *8,12,22, 27, and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restriction

The Election filed 7/27/07 in response to the Office Action of 6/20/07 is acknowledged and has been entered. Applicant elected, with traverse, group I and the following prognostic set: adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; Metallothionein 1H-like protein; and clone IMAGE: 5270727.

The traversal is on the ground(s) that the PCT examiner of the international stage of this application did not make a lack of unity finding. Further, in regards to restriction between group I and group II, Applicant argues that groups I and II of the presently amended application should be examined together because the pending claims contain a single expression profile and a method for determining the prognosis using a single prognostic set. Applicant further argues that under a proper consideration of unity of invention, there is no rationale for separating out claims to a polypeptide and a polynucleotide encoding it. Applicant further argues that a novel and inventive prognostic gene set represents a link between groups I and II and constitutes a single inventive concept under PCT Rule 13.1. Applicant further points to MPEP 803 and presents (1) arguments based on an invention being independent and distinct and (2) arguments based on search burden. This is not found persuasive. In regards to the argument that the PCT examiner of the international stage of this application did not make a lack of unity finding, a finding of lack of unity for the instant application does not hinge on whether or not an a PCT examiner of the international stage of this application

demonstrated a lack of unity. Each application is examined on its own merits. In regards to the argument that groups I and II of the presently amended application should be examined together because the pending claims contain a single expression profile and a method for determining the prognosis using a single prognostic set, the pending claims do not contain a single expression profile and a method for determining prognosis using a single prognostic set. The pending claims are drawn to products for detecting multiple polynucleotides, products for detecting multiple polypeptides, methods of determining prognosis by detecting multiple polynucleotides, and methods of determining prognosis by detecting multiple polypeptides. Further, in regards to the argument that there is no rationale for separating out claims to a polypeptide and a polynucleotide encoding it, the instant claims are not merely product claims drawn to a single polypeptide and a single polynucleotide encoded by said polypeptide, the instant inventions comprise products for detecting multiple polynucleotides, products for detecting multiple polypeptides, methods of determining prognosis by detecting multiple polynucleotides, and methods of determining prognosis by detecting multiple polypeptides. In regards to the argument that a novel and inventive prognostic gene set represents a link between groups I and II and constitutes a single inventive concept under PCT Rule 13.1, the gene set is not the claimed invention. The claimed inventions comprise products for detecting multiple polynucleotides, products for detecting multiple polypeptides, methods of determining prognosis by detecting multiple polynucleotides, and methods of determining prognosis by detecting multiple polypeptides. Further, in regards to the arguments based on MPEP 803, such arguments do not apply when

restriction is required under 35 USC 121 and 372, as in the instantly filed application. Thus, when the Office considers international applications as an International Searching Authority, as an International Preliminary Examining Authority, and during the national stage as a Designated or Elected Office under 35 U.S.C. 371, PCT Rule 13.1 and 13.2 will be followed when considering unity of invention of claims of different categories without regard to the practice in national applications filed under 35 U.S.C. 111.

Further, the inventions listed as groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking groups I-II appears to be that they all relate to the special technical feature of a prognostic set for determining the prognosis of a patient with breast cancer. However, Wirtz et al (US 2004/0018525 A1; 1/29/04) teaches a prognostic set for determining the prognosis of a patient with breast cancer (see the Affymetrix U133 chip taught at paragraph 487 and the methods of Example 1, in particular). Therefore, the technical feature linking the inventions of groups I-II does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art. Accordingly, groups I-II are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

Applicant is again reminded that the restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claims 1, 12, 16, 23, 28, and 32. Upon the allowance of the linking claim(s), the restriction requirement as to the

linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/ are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1, 2, 5-20, and 22-37 are pending and are currently under consideration.

Specification

The specification is objected to because it contains embedded hyperlinks and/or other form of browser-executable code (pages 23 and 56, in particular). Applicant is required to delete all embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. The claims define the

invention by Unigene numbers corresponding to gene descriptions (see Table S6, in particular), which are not sequences provided in the specification. The sequences of the Unigene numbers corresponding to gene descriptions are essential to practice the claimed invention, and the only disclosure of the sequences is made by references to published information outside of the specification. Therefore, information essential to practice the invention is incorporated by reference. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Objections

Claim 8 is objected to for reciting the acronym "NPI". The specification indicates "NPI" means Nottingham Prognostic Index (see page 1, in particular). In order to be consistent with the specification, amending claim 8 to replace "high NPI or low NPI" with "high **Nottingham Prognostic Index (**NPI**)** or low NPI" would obviate this objection.

Claim 12 is objected to for the following awkward recitation: "Apparatus for assigning a prognosis to a breast tumour sample...". There appears to be an article missing before "Apparatus". It is suspected Applicant may have intended claim 12 to

recite: "**An** ~~A~~apparatus for assigning a prognosis to a breast tumour sample...". Appropriate correction is required.

Claim 22 is objected to because of an apparent typographical error. Claim 22 recites: "A kit according to claims 16 comprising...". It is suspected Applicant intended claim 22 to recite: "A kit according to claim~~s~~ 16 comprising...". Appropriate correction is required.

Claim 27 is objected to because of an apparent typographical error. The word "and" appears to be missing before "(C)". Appropriate correction is required.

Claim 28 is objected to because of an apparent typographical error. Claim 28 recites "datacarrier". It is suspected Applicant intended claim 28 to recite: "data carrier". Proper correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 28-31 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 28-31 are drawn to expression profile databases retrievably held on a datacarrier.

In order to fall within a statutory category, the "datacarrier" of claim 28 must *only* reasonably be interpreted by one or ordinary skill as something which has necessary structure for it to be a manufacture or machine. In the instant case, the specification discloses possible examples of data carriers (including communication and propagation media stored in a computer; see page 36, in particular); however, the instant specification does not limit the "datacarrier" of claim 28 to reasonably be interpreted by one or ordinary skill as something which has necessary structure for it to be a manufacture or machine. One of skill in the art would interpret "datacarrier" to reasonably include forms of energy such as light waves or other forms of carrier waves, which do not fall within a statutory category, and cables, wires and fibers, which while seemingly a manufacture would not act as a computer component and enable any functionality to the database to be realized absent positive recitation in the claims of the necessary hardware to receive and convert the signals for use by a processor. *Further*, it is noted that the databases of claims 28-31 are non-statutory due to the fact the profiles of the database are non-functional descriptive material, as claims 28-31 lack recitation of a functional relationship between data elements so as to constitute a true data structure and actually impart functionality. See MPEP 2106.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5-11, 13-15, 17-20, 22, 24-27, 29-31, and 33-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependent claims 2 and 5-11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims are drawn to a method for determining the prognosis of a patient with breast cancer "based on" the expression levels of a prognostic set of genes including adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727; however, it is unclear what kind of result (such as what kind of expression levels) would be indicative of what kind of prognosis for a patient with breast cancer. The omitted steps are: correlating a specific result to a specific prognosis.

Claims 2, 5, 8, 9, 11 and dependent claims 6, 7, and 10 are rejected for reciting: "A method according to claim 1...". It is unclear whether claims 2, 5, 8, 9, and 11 are further limiting the entire method of claim 1, whether claims 2, 5, 8, 9, and 11 are further limiting a single method step of claim 1, or whether claims 2, 5, 8, 9, and 11 are somehow related to claim 1 according to another way. To obviate this rejection, Applicant may amend claims 2, 5, 8, 9, and 11 to recite: "**A** **The** method ~~**according to**~~ **of** claim 1...".

Claims 2, 13, 14, 17, 24, and 29 are rejected for attempting to claim methods or products by making reference to a table within the specification (Table S6). 35 U.S.C. 112, second paragraph, requires that the *claims* claim the subject matter. Reference to a table within the disclosure by a claim is not an acceptable method of claiming subject matter under 35 U.S.C. 112, second paragraph.

Claim 6 and dependent claim 7 are rejected for reciting: "A method according to claim 5...". It is unclear whether claim 6 is further limiting the entire method of claim 5, whether claim 6 is further limiting a single method step of claim 5, or whether claim 6 is somehow related to claim 5 according to another way. To obviate this rejection, Applicant may amend claim 6 to recite: "~~A~~ **The** method **of** ~~**according to**~~ claim 5...".

Claim 6 and dependent claim 7 are rejected because claim 6 recites"...said expression products obtained from the sample...". There is insufficient antecedent basis for this limitation in the claim.

Claim 7 is rejected for reciting: "A method according to claim 6...". It is unclear whether claim 7 is further limiting the entire method of claim 6, whether claim 7 is further limiting a single method step of claim 6, or whether claim 7 is somehow related to claim 6 according to another way. To obviate this rejection, Applicant may amend claim 7 to recite: "~~A~~ **The** method ~~**according to**~~ **of** claim 6...".

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 8 is drawn to a method comprising classifying a sample of a breast tumour as having either a high NPI, a low NPI, a good prognosis, or a bad prognosis; however, claim 8 does not indicate which particular result(s) indicate that a sample has a particular classification. The omitted steps are: indicating which specific result(s) correlate with which particular classification.

Claim 10 is rejected for reciting: "A method according to claim 9...". It is unclear whether claim 10 is further limiting the entire method of claim 9, whether claim 10 is further limiting a single method step of claim 9, or whether claim 10 is related to claim 9 according to another way. To obviate this rejection, Applicant may amend claim 10 to recite: "**~~A~~ The** method **~~according to~~ of** claim 9...".

Claims 13-15 are rejected for reciting: "Apparatus according to claim 12...". It is unclear whether claims 13-15 are further limiting the product of claim 12, whether claims 13-15 are reciting products somehow related to the apparatus of claim 12, or whether claims 13-15 are related to claim 12 according to another way. To obviate this rejection, Applicant may amend claims 13-15 to recite: "**The a~~A~~**pparatus **~~according to~~ of** claim 12...".

Claims 17-20 and 22 are rejected for reciting: "A kit according to claim 16..." or "A kit according to claims 16...". It is unclear whether claims 17-20 and 22 are further limiting the product of claim 16 or whether claims 17-20 and 22 are reciting products somehow related to the kit of claim 16. To obviate this rejection, Applicant may amend claims 17-20 and 22 to recite: "~~A~~ **The** kit ~~according to~~ **of** claim~~s~~ 16...".

Claim 22 is rejected for reciting: "...comprising nucleotide primers capable of binding to the expression products of the genes of the prognostic set such that they can be amplified by PCR". It is unclear what is meant by "they". It is unclear whether "they" means: (1) "nucleotide primers capable of binding to the expression products of the genes of the prognostic set", (2) "the expression products of the genes", or (3) "the genes".

Claims 24-26 and dependent claim 27 are rejected for reciting: "A method according to claim 23...". It is unclear whether claims 24-26 are further limiting the entire method of claim 23, whether claims 24-26 are further limiting a single method step of claim 23, or whether claims 24-26 are related to the method of claim 27 according to another way. To obviate this rejection, Applicant may amend claims 24-26 to recite: "~~A~~ **The** method ~~according to~~ **of** claim 23...".

Claim 27 is rejected for reciting: "A method according to claim 26...". It is unclear whether claim 27 is further limiting the entire method of claim 26, whether claim 27 is

further limiting a single method step of claim 26, or whether claim 27 is related to the method of claim 26 according to another way. To obviate this rejection, Applicant may amend claim 27 to recite: "~~A~~ **The** method ~~according to~~ **of** claim 26...".

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 27 is drawn to a method comprising comparing first and second expression profiles to determine the prognosis of a first breast tumour sample. The omitted steps are: correlating a particular result (such as a particular relationship based on a particular comparison) with a breast tumour sample that has a particular prognosis.

Claims 29-31 are rejected for reciting: "An expression profile database according to claim 28...". It is unclear whether claims 29-31 are further limiting the database of claim 28 or whether claims 29-31 are reciting databases somehow related to the database of claim 28. To obviate this rejection, Applicant may amend claims 29-31 to recite: "~~An~~ **The** expression profile database ~~according to~~ **of** claim 28...".

Claim 31 recites the limitation "the source tumour". There is insufficient antecedent basis for this limitation in the claim.

Claims 33-37are rejected for reciting: "A method according to claim 32...". It is unclear whether claims 33-37 are further limiting the entire method of claim 32, whether claims 33-37 are further limiting a single method step of claim 32, or whether claims 33-37 are somehow related to claim 32 according to another way. To obviate this rejection, Applicant may amend claims 33-37 to recite: "**~~A~~ The** method **of** ~~**according to**~~ claim 32...".

Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 36 recites: "...providing expression profiles from the tumour at different stages of treatment and said expression profiles to determine a change in prognostic class". There is an active step missing between the words "and" and "said" which would describe what one is to do with "said expression profiles".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-11, and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining the prognosis of a first patient with breast cancer comprising comparing the polynucleotide expression levels of a set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1,

Metallothionein 1H-like protein, and clone IMAGE: 5270727 in a breast tumor sample from said first patient to the expression levels of the polynucleotides of said set of genes in a breast tumor sample from a second patient, wherein a first patient with higher levels of expression of polynucleotides of said set of genes has a poorer prognosis than a second patient with lower levels of expression of said set of genes (see page 4 and Table S6, in particular), the specification does not reasonably provide enablement for a method for determining the prognosis of a patient with breast cancer comprising assigning a prognosis to the patient "based on", in every way, just any type of expression level in a breast tumour of said patient of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727, and optionally comprising determining ER and/or Erb2 status of the tumour sample (see claim 1) or a method of determining, in just any way, the prognosis of a first breast tumour sample by comparing just any type of expression profiles of just any first and second tumour samples of known prognoses (see claim 27). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence

or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a method for determining the prognosis of a patient with breast cancer comprising assigning a prognosis to the patient "based on", in every way, just any type of expression level in a breast tumour of said patient of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727, and optionally comprising determining ER and/or Erb2 status of the tumour sample (see claim 1) and a method of determining, in just any way, the prognosis of a first breast tumour sample by comparing just any type of expression profiles of just any first and second tumour samples of known prognoses (see claim 27).

The specification teaches a method for determining the prognosis of a first patient with breast cancer comprising comparing the polynucleotide expression levels of a set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 in a breast tumor sample from said first patient to the expression levels of the polynucleotides of said set of genes in a breast tumor sample from a second patient, wherein a first patient with higher levels of expression of polynucleotides of said set of genes has a poorer prognosis than a second patient with lower levels of expression of said set of genes (see page 4 and Table S6, in particular). The specification does not demonstrate that an analysis of polypeptide expression of a

set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 would predictably determine a prognosis.

The state of the prior art dictates that if expression of a molecule, such as a specific polynucleotide, is to be used as a surrogate for a particular prognostic state, some prognostic state must be identified in some way with expression of said molecule. There must be some expression pattern that would allow expression of the molecule to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a

valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the molecule's expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use expression of the molecule in as an indication of a particular prognosis without undue experimentation.

Further, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well

defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Thus, the predictability of protein translation and its possible utility as a prognostic cannot predictably be determined by levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Thus, information obtained from expression profiles of mRNA expression products, such as expression products of adenine phosphoribosyltransferase genes, MCM4 minichromosome maintenance deficient 4 (S. cervisiae) genes, exonuclease 1 genes, Metallothionein 1H-like protein genes, and clone IMAGE: 5270727 genes, only serves as the basis for further research on the observation itself and is not predicative of polypeptide expression levels.

The level of unpredictability for determining a particular prognosis based on expression levels of genes is quite high. Since neither the specification nor the prior art provide evidence that a measurement of just any type of expression levels of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 is predictably indicative, in every way, of every prognosis, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association.

Further, since neither the specification nor the prior at provide evidence that a comparison of just any type of expression profiles of just any first and second tumour samples of known prognoses would be indicative of, in every way, the prognosis of a first breast tumour sample, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for determining the prognosis of a patient with breast cancer comprising assigning a prognosis to the patient "based on", in every way, just any type of expression level in a breast tumour of said patient of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727, and optionally comprising determining ER and/or Erb2 status of the tumour sample (see claim 1) and a method of determining, in just any way, the prognosis of a first breast tumour sample by comparing just any type of expression profiles of just any first and second tumour samples of known prognoses (see claim 27), and Applicant has not enabled said methods because it has not been shown that (1) any expression levels of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 are predictably indicative, in every way, of every prognosis or (2) that a comparison of

expression profiles of just any first and second tumour samples of known prognoses would be indicative of, in every way, the prognosis of a first breast tumour sample.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 12, 13, 15-20 and 22, 28-37are rejected under 35 U.S.C. 102(e) as being anticipated by Wirtz et al (US 2004/0018525 A1; filed 5/9/03).

Claim 12 is drawn to an apparatus comprising a solid support to which are attached binding members, each binding member being capable of specifically and independently binding to an expression product of a prognostic set of genes comprising adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; Metallothionein 1H-like protein; and clone IMAGE: 5270727. It is noted that claim 12 requires that the claimed kit comprises binding

members capable of specifically binding to "**an** expression product of" one of a prognostic set of genes. Claim 12 does not require that the kit comprise binding members capable of specifically binding one of **each** of the **complete** polynucleotides encoded by the genes recited in claim 12 since any type of expression product of the recited genes is required to be bound by binding memers. Claim 13 is drawn to an apparatus according to claim 12, wherein the prognostic set comprises at least 5, 10, 20, 30, 40, 50, 60 or all of the genes of Table S6. Claim 15 is drawn to an apparatus according to claim 12, comprising a nucleic acid microarray wherein the binding members are nucleic acid sequences. Claim 16 is drawn to a kit for assigning a prognosis to a patient with breast cancer, said kit comprising a plurality of binding members capable of specifically binding to expression products of genes of a prognostic set of genes and a detection reagent, wherein the prognostic set includes adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; Metallothionein 1H-like protein; and clone IMAGE: 5270727, said kit optionally comprising the apparatus of claim 12. It is noted that claim 16 requires that the claimed kit comprises binding members capable of specifically binding to "expression products of" one of a prognostic set of genes. Claim 16 does not requires that the kit comprise binding members capable of specifically binding one of each of the **complete** polynucleotides encoded by the genes recited in claim 16 since any type of expression product of the recited genes is required to be bound by binding members. Claim 17 is drawn to a kit according to claim 16, wherein the prognostic set comprises at least 5, 10, 20, 30, 40, 50, 60 or all of the genes of Table S6. Claim 18 is

drawn to a kit according to claim 16, further comprising a data analysis tool, wherein the data analysis tool is a computer program. Claim 19 is drawn to a kit according to claim 18, wherein the data analysis tool comprises an algorithm adapted to discriminate between expression profiles of tumours with differing prognosis. Claim 20 is drawn to a kit according to claim 16 comprising the expression profiles from breast tumour samples with known prognoses and/or expression profiles characteristic of a particular prognosis. Claim 22 is drawn to a kit according to claim 16 comprising nucleotide primers "capable of" binding to the expression products of the genes of the prognostic set "such that" "they" can be amplified in PCR. Claim 28 is drawn to an expression profile database comprising a plurality of gene expression profiles of breast tumour samples, wherein the gene expression profiles are "derived from" the expression levels of a prognostic set of genes "comprising" adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; Metallothionein 1H-like protein; and clone IMAGE: 5270727, which database is retrievably held on a datacarrier. Due to the "derived from" language recited in claim 28, it is noted that claim 28 does not require that the gene expression profiles comprise information regarding the expression levels of all (or any) of the genes recited in claim 28. Claim 29 is drawn to an expression profile database according to claim 28, wherein the prognostic set comprises at least 10, 20, 30, 40, 50, 60 or all of the genes of Table S6. Claim 30 is drawn to an expression profile database according to claim 28, wherein the expression profiles are nucleic acid expression profiles. Claim 31 is drawn to an expression profile database according to claim 28, wherein he expression profiles are categorized

according to the ER status of the source tumour. Claim 32 is drawn to a method for identifying a set of genes that are differentially expressed within a group of tumours, the method including providing an expression profile from each of a plurality of tumours of the group, classifying the profiles according to molecular subtype of tumour, and analyzing expression profiles within a subtype to identity a discriminating set of genes, wherein the genes of the discriminating set are differentially expressed within that subtype. Claim 33 is drawn to a method according to claim 32 further comprising steps to assign a class to a tumour sample from a patient, wherein differential expression of genes of the discriminating set are characteristic of the class, the steps including providing expression levels in the sample of the discriminating set, and assigning a class to the tumour based on the expression levels. Claim 34 is drawn to a method according to claim 32 comprising the steps of determining the expression levels of the genes of the discriminating set in a tumour sample, determining an expression profile from the expression levels and adding the profile to a database. Claim 35 is drawn to a method according to claim 32 wherein the molecular subtype of the tumour sample is also identified and added to the database. Claim 36 is drawn to a method according to claim 32 providing expression profiles from the tumour at different stages of treatment and said expression profiles to determine a change in prognostic class, wherein the expression profiles are derived from the expression levels of genes of the discriminating set. Claim 37 is drawn to a method according to claim 32 wherein the tumours are breast tumours and the molecular subtype corresponds to the ER status of the tumour.

Wirtz et al teaches a prognostic set for determining the prognosis of a patient with breast cancer (see the Affymetrix U133 apparatus taught at paragraph 487 and the methods of Example 1, in particular). As indicated by the instant specification (see page 23, in particular) and as taught at www.affymetrix.com as of 8/26//07, the Affymetrix U133 apparatus comprises a nucleic acid microarray wherein the binding members are nucleic acid sequences designed to detect polynucleotide expression of tens of *thousands* of genes, including the following genes: adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; and Metallothionein 1H-like protein. Further, it is noted that the binding members of the Affymetrix U133 would bind "expression products", such as fragments, of polynucleotides encoded by clone IMAGE: 5270727. Wirtz et al further teaches an apparatus comprising a solid support to which are attached binding members, each binding member being capable of specifically and independently binding to an expression product of a prognostic set of genes comprising adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; Metallothionein 1H-like protein; and clone IMAGE: 5270727 (see paragraphs 304-316 and the Affymetrix U133 chip taught at paragraph 487, in particular). Further, said U133 apparatus taught at paragraph 487 comprises a prognostic set that comprises at least 5, 10, 20, 30, 40, 50, 60 or all of the genes of Table S6 (see page 74 of the instant specification or compare genes of Table S6 to the U133 chip database found as of 8/26//07 at www.affymetrix.com). Wirtz et al further teaches said U133 apparatus in a kit for assigning a prognosis to a patient with breast

cancer, said kit comprising a plurality of binding members capable of specifically binding to expression products of genes of a prognostic set of genes and a detection reagent, wherein the prognostic set includes adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; and Metallothionein 1H-like protein (see paragraphs 304-316 and the U133 chip database found as of 8/26//07 at www.affymetrix.com, in particular). Wirtz et al further teaches said kit further comprising a data analysis tool, wherein the data analysis tool is a computer program (paragraphs 317-339, in particular). Wirtz et al further teaches said kit wherein said data analysis tool comprises an algorithm adapted to discriminate between expression profiles of tumours with differing prognosis (paragraph 336, in particular). Wirtz et al further teaches said kit comprising the expression profiles from breast tumour samples with known prognoses and/or expression profiles characteristic of a particular prognosis (see paragraphs 336, paragraph 463, and Example 1, in particular). Wirtz et al further teaches a kit according to claim 16 comprising nucleotide primers "capable of" binding to the expression products of the genes of the prognostic set "such that" "they" can be amplified in PCR (see paragraph 484, in particular). Wirtz et al further teaches a nucleic acid expression profile database, created by using the U133 kit, comprising a plurality of gene expression profiles of breast tumour samples, wherein the gene expression profiles are "derived from" the expression levels of a prognostic set of genes "comprising" adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; Metallothionein 1H-like protein; and clone IMAGE: 5270727; which database is retrievably held on a

datacarrier (see paragraphs 336, paragraph 463, and Example 1, in particular). Again, it is noted that instant claim 28 does not require that the gene expression profiles comprise information regarding the expression levels of *any* of the genes recited in claim 28. Wirtz et al further teaches an expression profile database, wherein the expression profiles are categorized according to the ER status (paragraph 2, in particular). Wirtz et al further teaches a method for identifying a set of genes that are differentially expressed within a group of tumours, the method including providing an expression profile from each of a plurality of tumours of the group, classifying the profiles according to molecular subtype of tumour (such as a subtype of tumor that is responsive to a particular therapeutic), and analyzing expression profiles within a subtype to identity a discriminating set of genes, wherein the genes of the discriminating set are differentially expressed within that subtype (see Example 1, in particular). Wirtz et al teaches a method further comprising steps to assign a class to a tumour sample from a patient (such as a class that would respond to a therapeutic), wherein differential expression of genes of the discriminating set are characteristic of the class, the steps including providing expression levels in the sample of the discriminating set, and assigning a class to the tumour based on the expression levels (paragraph 324, in particular). Wirtz et al further teaches a method comprising the steps of determining the expression levels of the genes of the discriminating set in a tumour sample, determining an expression profile from the expression levels, wherein the molecular subtype of the tumour sample is also identified, and adding the profile and the molecular subtype to a database (pages 33-34, in particular). Wirtz et al further teaches providing expression

profiles from the tumour at different stages of treatment, wherein the expression profiles are derived from the expression levels of genes of the discriminating set (see paragraphs 60, 64, 324, and 328, in particular). Wirtz et al further teaches methods wherein the tumours are breast tumours and the molecular subtype corresponds to the ER status of the tumour (paragraph 2, in particular).

Summary

Claim 23 is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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